Cancer Causes and Control, 4, 477 - 482

A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States)

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(Received 28 April 1993; accepted in revised form 9 June 1993)

Risk factors for pancreatic cancer were evaluated in a cohort study of 17,633 White men in the United States who responded to a mailed questionnaire in 1966 and were followed-up through 1986 for mortality. Cigarette smoking and alcohol consumption were found to be important risk factors for pancreatic cancer. Risks increased significantly with number of cigarettes smoked, reaching fourfold for smokers of 25 or more cigarettes per day relative to nonsmokers. Alcohol intake also was related significantly to risk, with consumers of 10 or more drinks per month having three times the risk of nondrinkers, but dose-response trends among drinkers were not smooth. Coffee consumption was unrelated to risk. Dietary analyses revealed a rising rate of pancreatic cancer mortality with increasing consumption of meat after adjustment for other risk factors. Men in the highest quartile of meat intake had about three times the risk of those in the lowest quartile. No consistent association, however, was observed for consumption of fruits, vegetables, or grains. This study confirms cigarette smoking as an important risk factor for pancreatic cancer, and provides evidence that elevated intake of alcohol and meat may increase the risk of this fatal malignancy.

Key words: Alcohol drinking, coffee, cohort study, diet, mortality, pancreatic neoplasm, tobacco, United States, White males.

Introduction

Cancer of the pancreas is a rapidly fatal malignancy, with over 90 percent of patients dead within one year of diagnosis.[1,2] In the United States, pancreatic cancer causes about 25,000 deaths annually and is ranked as the fifth leading cause of cancer death.[1] The etiology of this malignancy is largely unknown, with cigarette smoking being the only established risk factor.[1-8] Among other exposures, diet may be important.[1,2] High intake of animal foods[6,9-12] or fat and protein, [12-14] and low fruit/vegetable consumption[6,9-11,15-17] have been associated with increased risk of pancreatic cancer in some epidemiologic studies, while carbohydrate intake was implicated in a recent multicenter study.[18] Alcohol, coffee consumption, certain occupational exposures

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(e.g., petroleum products), diabetes mellitus, and familial occurrence also have been linked to the risk of pancreatic cancer, but results are inconsistent.[1,2,10,19,20] Most previous epidemiologic investigations have used retrospective designs with a high proportion of next-of-kin respondents, which may affect the reporting of previous exposures, particularly diet. Herein, we report results from a cohort study, based on 20 years of mortality experience for 17,633 White US men, to evaluate the effects of tobacco, alcohol, and diet on the risk of pancreatic cancer.

Materials and methods

This cohort study was conducted among life-insurance policy holders of the Lutheran Brotherhood Insurance Society (LBS). In October 1966, a questionnaire was sent to 26,030 White male policy holders who were 35 years of age or older and lived in California, New Jersey, Washington, and the north central states of Michigan, Minnesota, Missouri, North Dakota, Ohio, and Wisconsin. A total of 17,818 (68.5 percent) men completed the questionnaire and were included in the cohort and followed-up for mortality. Death certificates for study participants were received semiannually from LBS and coded by a nosologist for underlying cause of death, other contributory causes of death, and other significant conditions. By 1986, after 20 years of follow-up, 4,513 deaths (26 percent of the cohort) occurred among active policy holders, including 1,033 cancer deaths. Fifty-seven deaths were due to pancreatic cancer (ICD-9[21] code 157), accounting for 5.5 percent of cancer deaths. Another 4,027 subjects (23 percent) were lost to follow-up due to maturation or lapse of their policies. In total, there were 286,731 person-years of follow-up.

A self-administered structured questionnaire was used to elicit information on tobacco and alcohol use, dietary habits, and demographic characteristics in 1966. Diet was assessed by asking the frequency of current consumption of 35 food items, which were then combined into food groups based on similarity in nutrient contents or botanic characteristics. These food variables were categorized into four levels according to the quartile distribution of intake of all cohort members. Total caloric intake, as a categorical variable in the Poisson regression model, was adjusted for in dietary analyses to reduce potential variations that may arise from exaggeration or under-reporting of food consumption by some study participants. This caloric intake index was computed using information on average portion size and nutrient composition derived from the Second National Health and Nutrition Examination Survey (NHANES II)[22] and from US Department of Agriculture food composition tables,[23] respectively. One hundred eighty-five respondents (one percent) were excluded from dietary analyses because of missing data on more than 10 food items. Seventy-one percent of the respondents had no missing data and for the 29 percent with 10 or fewer missing food items, 87 percent had fewer than five missing items. We used the median intake value of the remaining respondents for imputation, stratified by urban/rural, educational attainment, and age categories. An additional 1,656 respondents (nine percent), including three pancreatic cancer deaths, were excluded because they reported being on a special diet at the time of data collection.

Relative risks (RR) were used to measure the association between pancreatic cancer mortality and study factors. Multiple Poisson regression was applied to control for potential confounders and to derive adjusted RRs and 95 percent confidence intervals (CI).[24,25] Trends in risk were evaluated by treating ordinal score variables as continuous variables in the Poisson regression model. All statistical tests were based on a two-tail probability.

Results

Table 1 presents the risk of pancreatic cancer mortality associated with tobacco and alcohol use. A significant dose-response effect of cigarette smoking was observed, with a fourfold risk of pancreatic cancer among current heavy smokers (RR = 3.9, CI = 1.5-10.3). The risks, however, were not elevated for ex-smokers or for those who had exclusively used tobacco other than cigarettes (Table 1). Among ever-users of smokeless tobacco, the age-, alcohol-, and smoking-adjusted risk was increased, although not statistically significant (RR = 1.7, CI = 0.9-3.1), based on 16 deaths. Alcohol consumption was not high (only 26 percent of the men reported having 10 or more drinks per month, or 2.5 drinks per week). There was a significantly elevated risk of pancreatic cancer (RR = 2.4, CI = 1.1-5.5) among drinkers, and risks tended to increase with intake of both beer and hard liquor, as well as total number of alcoholic drinks, although after adjustment for smoking the trends were less pronounced. Further adjustment for cigarette smoking using finer categories of use did not change the risk estimates. All but four of the pancreatic cancer subjects who drank alcohol consumed both beer and hard liquor. Exposure to both smoking (≥ 25 cigarettes/day) and alcohol (≥ 3 drinks/month) was associated with an RR of 6.6 (CI = 2.2-20.5, based on seven

Table 1. Relative risks (RR) of pancreatic cancer mortality by use of tobacco and alcohol in the Lutheran Brotherhood cohort, 1966-86

Exposure variable	No. of deaths	Person-years	RR[a]	RR[b]	(CI)[c]
Tobacco use					
Never used any tobacco	9	58,888	1.0	1.0	—
Used tobacco other than cigarettes	5	27,025	0.9	0.8	(0.3-2.5)
Cigarette smokers					
Ex-smokers	19	99,353	1.2	1.0	(0.4-2.2)
<25 cigarettes/day	12	68,510	1.4	1.4	(0.6-3.2)
25+ cigarettes/day	8	21,604	4.1	3.9[d]	(1.5-10.3)
Alcohol use					
Never	7	59,818	1.0	1.0	—
Ever	49	222,060	2.6	2.4	(1.1-5.5)
Beer use (times/mo)					
<3	19	91,614	2.4	2.2	(0.9-5.5)
3-13	17	67,700	3.3	3.1	(1.2-7.8)
14+	8	29,818	3.7	3.3[d]	(1.1-9.6)
Hard liquor use (times/mo)					
<3	25	100,460	3.2	3.1	(1.3-7.4)
3-13	12	53,396	2.9	2.6	(1.0-7.0)
14+	6	19,693	3.9	3.3[d]	(1.1-10.5)
Total alcoholic drinks (times/mo)					
<3	13	74,440	2.0	2.0	(0.8-5.2)
3-9	13	44,594	3.7	3.6	(1.4-9.3)
10+	18	72,005	3.4	3.1[d]	(1.2-8.0)

[a] Adjusted for age.
[b] Adjusted for age and alcohol index for smoking variables; and age and smoking index for alcohol use variables. Smoking index was defined as: never smoked cigarettes; light: currently smoked < 25 cigarettes/day or ex-smokers; heavy smokers: currently smoked 25+ cigarettes/day. Alcohol index was defined as: never used any alcohol; light drinkers: < 3 times alcohol/month; heavy drinkers, 3+ times alcohol/month.
[c] CI = 95% confidence interval.
[d] Trend test $P \leq 0.01$.

Table 2. Relative risks (RR) of pancreatic cancer mortality by coffee consumption in Lutheran Brotherhood cohort, 1966-86

Coffee consumption (cups/day)	No. of deaths	Person-years	RR[a]	RR[b]	(CI)[c]
<3	21	87,784	1.0	1.0	—
3-4	18	107,580	0.7	0.6	(0.3-1.2)
5-6	12	63,464	1.0	0.7	(0.4-1.6)
7+	5	26,490	1.2	0.9	(0.3-2.4)

[a] Adjusted for age.
[b] Adjusted for age, smoking index, and alcohol index.
[c] CI = 95% confidence interval.

deaths). In contrast, coffee consumption was unrelated to risk (Table 2). Coffee drinking among nonsmokers also was not associated with risk.

High consumption of animal foods, except for eggs and dairy, was associated with increased risk of pancreatic cancer (Table 3). A dose-response relationship was evident for consumption of meat, with RRs of 1.0, 1.4, 1.8, and 3.0 from low to high intake groups. Salted/smoked meat/fish intake also was associated with increased risks, although the trend test was not significant. Risk for consumption of vegetables, fruits, and bread/cereal showed no clear association with pancreatic cancer. Exclusion of pancreatic cancer deaths that occurred in the first five years of follow-up did not change the findings materially for diet, coffee intake, alcohol consumption, or cigarette smoking.

Further analyses were performed to examine possible joint effects of meat consumption with cigarette smoking and alcohol drinking (Table 4). Positive associations of meat consumption with pancreatic cancer were found in all strata of cigarette smoking and alcohol drinking.

Discussion

Our cohort study supports previous investigations

Table 3. Relative risks (RR) of pancreatic cancer mortality by consumption levels of animal food groups in the Lutheran Brotherhood cohort, 1966-86

Food items	Relative risk[a] by consumption levels (Quartile)				*P*-value from trend test
	Q_1 (low)	Q_2	Q_3	Q_4 (high)	
All meat	1.0	1.4 (0.6-3.4)[b]	1.7 (0.7-4.2)	3.0 (1.2-7.5)	0.02
Red meat	1.0	1.1 (0.4-2.6)	1.8 (0.8-4.3)	2.4 (1.0-6.1)	0.03
Chicken	1.0	0.9 (0.3-2.5)	1.0 (0.4-2.6)	1.9 (0.7-5.5)	0.13
All fish	1.0	1.2 (0.5-3.0)	2.0 (0.8-4.7)	1.4 (0.6-3.7)	0.26
Eggs and dairy	1.0	0.9 (0.4-1.9)	0.9 (0.4-2.2)	0.7 (0.2-2.2)	0.63
Salted/smoked meat/fish	1.0	1.0 (0.4-2.3)	1.2 (0.5-2.9)	1.5 (0.6-3.4)	0.28

[a] Adjusted for age, smoking index, alcohol index and total calories.
[b] 95% confidence interval.

Table 4. Relative risks (RR) of pancreatic cancer mortality by consumption levels of total meat, cigarette smoking, and alcohol drinking in the Lutheran Brotherhood cohort, 1966-86

Cigarette/alcohol use	Meat consumption[a]					
	Low			High		
	No. of deaths	RR	(CI)[b]	No. of deaths	RR	(CI)[b]
Cigarette smoking[c]						
Never	6	1.0[d]	—	8	1.7	(0.6-5.2)
Light	12	1.1	(0.4-2.9)	16	1.6	(0.6-4.3)
Heavy	3	3.0	(0.7-12.5)	5	4.7	(1.3-16.7)
Alcohol drinking[c]						
Never	3	1.0[e]	—	4	2.2	(0.5-10.3)
Light	5	1.4	(0.3-5.8)	11	4.3	(1.1-16.4)
Heavy	13	3.9	(1.1-14.2)	16	4.8	(1.3-17.6)

[a] Classified by median intake among total cohort members.
[b] CI = 95% confidence interval.
[c] See footnote [b] in Table 1 for explanation.
[d] Adjusted for age, alcohol index and total calories.
[e] Adjusted for age, smoking index and total calories.

indicating that cigarette smoking is a major risk factor for pancreatic cancer.[1-8] The risks among current smokers at the time of the interview (1966) increased significantly with number of cigarettes smoked per day. There was little or no excess among ex-smokers, suggesting that cessation of smoking may lower risk of this cancer. The moderately elevated risk for smokeless tobacco is consistent with an earlier report on the cohort,[26] and results from a Norwegian cohort.[27] In agreement with most previous studies,[5-9,27-30] we found no association of coffee consumption with pancreatic cancer risk. This observation, based on data from a prospective study, provides additional evidence that coffee is not a risk factor for pancreatic cancer.

Alcohol consumption was associated significantly with pancreatic cancer mortality in our study, even though consumption levels were relatively low. Significant excess risks of pancreatic cancer among heavy drinkers have been reported from prospective studies in Norway[27] and Japan (for whiskey drinkers only).[31] In contrast, most surveys of alcoholics generally have failed to demonstrate a significant link to pancreatic cancer, although a recent cohort study of Swedish alcoholics reported elevated risks in both sexes.[32] Results from case-control studies are mixed,[5-10,28-30,33-36] with only some studies[6,7,35,36] showing a positive dose-response relation with alcohol use. This discrepancy may be partially due to differences in study design.[19] Moreover, in most of these studies a large proportion of cases were deceased, so next-of-kin interviews were conducted. Misclassification of alcohol exposure arising from next-of-kin interviews, although likely to be nondifferential, may further attenuate an association with disease risk. It is noteworthy that heavy alcohol consumption may induce chronic pancreatitis, a possible risk factor for pancreatic cancer.[2,37]

Our dietary analyses revealed a significant dose-res-

ponse relation between meat consumption and pancreatic cancer. This finding is consistent with results from a large cohort study in Japan, in which a significant excess risk of pancreatic cancer was associated with frequent meat intake.[31] A cohort study among Seventh-Day Adventists, however, did not observe such a relation, but meat consumption in this population is relatively low.[38] Several case-control studies have linked pancreatic cancer to high consumption of animal foods,[6,9-12] particularly beef.[6,9,12] It has been suggested that protein[12] and fat (particularly saturated fat),[13,14] which are high in most animal foods, play an etiologic role in pancreatic cancer, although dietary results from other studies are not consistent.[12] In some studies, carbohydrates,[18] or dietary markers of this nutrient, such as rice,[10] pastry,[39] and white bread,[17,39] have been linked to an increased risk of pancreatic cancer. In particular, a large, multicenter, case-control study of pancreatic cancer implicated carbohydrates, rather than fats or protein, as a key risk factor.[18] These results, however, might have been influenced by recent changes in eating habits, since cases may choose bland foods due to early symptoms of this malignancy, thus influencing dietary recall.[40] In our study, we were unable to assess associations of pancreatic cancer mortality with dietary fat, protein, carbohydrate, and other nutrients, since our questionnaire included only 35 food items, and did not capture sufficient dietary sources of these nutrients. However, we found that high consumption of bread and cereal, a major source of carbohydrates, was unrelated to the risk of pancreatic cancer.

The mechanism for a positive association of pancreatic cancer mortality and meat consumption is not well understood, but high levels of fat and protein in meat can stimulate release of gastrointestinal hormones, including cholecystokinin (CCK), an important regulatory peptide for growth and secretion of the pancreas.[41] In experimental animals, CCK administration has induced pancreatic hypertrophy and cellular transformation.[42] In addition, cooked meat may contain other carcinogens such as polycyclic hydrocarbons and heterocyclic amines.[43]

High consumption of certain fruits and vegetables has been shown to be protective for pancreatic cancer in some previous studies,[6,9-11,15-17] but we did not find such an effect. Since dietary data were collected only once (in 1966), many cohort members could have changed their eating habits during the 20 years of follow-up. Because such misclassification of exposure is likely to be nondifferential, it would bias the RRs towards 1.0 and blunt a weak or even moderate association with certain dietary factors.

There were certain other limitations of our study. As with dietary information, no further data for smoking and alcohol use were available after the initial self-administered interviews in 1966. If smokers in this cohort followed the trend among American men in the past decades,[44] a substantial proportion of the cohort members may have stopped smoking during the 20 years of follow-up, although they still would be classified as current smokers in this analysis. This may result in an underestimate of the smoking effect. In addition, about one-fifth of the cohort members ($n = 4,027$) were lost to follow-up due to lapsed or matured policies, although there were no significant differences in tobacco, alcohol, or dietary intake between active members and those lost to follow-up at 20 years.[45] A special study to assess vital status of those lost to follow-up at 11.5 years detected no significant difference in cancer mortality between these two groups.[46] Thus, it is unlikely that incomplete follow-up could have substantially biased our results.

In summary, our cohort study confirms findings from previous studies that cigarette smoking is a major risk factor for pancreatic cancer. Alcohol and meat intake also were observed to increase risk, although further studies are needed to clarify these associations and the mechanisms involved.

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